COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 06.06.2023

Substance name: sodium bromide
CAS number: 7647-15-6
EC number: 231-599-9
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	1
Comment received				
Three separate CLH proposals were submitted for a group of inorganic bromide salts (sodium, potassium and calcium bromide). Read-across between these substances was performed in the dossiers. Another read-across substance, ammonium bromide (EC no. 235-183-8), was added to Table 3, Annex VI of the CLP regulation in February 2022 with a harmonised classification as Repr. 1B (FD), Lact., Eye Irrit. 2, STOT SE 3 and STOT RE 1. The read-across is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2023	Austria	The International Bromine Council BSEF	Industry or trade association	2
Comment received				
The International Bromine Council BSEF herewith provides comments on the CLH report and the proposed harmonized classification of sodium bromide as prepared by the Swedish Chemicals Agency. These comments are accompanied by a new toxicokinetic study to provide further supporting evidence for the classification proposed by BSEF on the endpoint reproductive toxicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BSEF detailed comments on KEMI CLH report NaBr_2023-06-01.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH Report NaBr - Supporting studies for CL.zip				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	United Kingdom	<confidential>	Company-Downstream user	3
Comment received				
The current proposal for classification of Sodium Bromide in Category Reproductive 1B is				

based on rationale that the adverse effects seen in high dose animal studies could be relevant to humans. While at present the focus in on assessing only the hazard properties of the substance we are urging that the rationale be reconsidered for the following reasons:
1) Sodium bromide is a critical part of a biocidal programme to control micro-organisms in water systems. It is non-volatile, is delivered to use sites in ways that prevent exposure and are applied to water systems using controlled dispensing systems. Thus, it is unlikely to cause any oral, inhalation, or dermal exposures to humans that are of toxicological significance.
2) In addition to being ubiquitous in the environment, bromine is an essential trace element that provides vital benefits to humans at low doses. Moreover, allowable daily intake levels have been established for bromine. Typical human exposures result in a beneficial human response versus an adverse human response.
Based on the factors cited above and detailed in our comments below, a Category 2 Classification for Reproductive Toxicity is more appropriate.

Introduction
These comments are in response to the public consultation on the Swedish Chemical Agency's proposal for harmonised classification for Sodium Bromide (CAS# 7647-15-6) in accordance with Annex VI of CLP Regulation (EC 1272/2008). We have reviewed the proposal as well as considered the special case of sodium bromide is a critical part of a biocidal programme to control micro-organisms in water systems. Four factors led to our conclusion that a Category 2 Classification for Reproductive Toxicity is more appropriate.
Figure 1*: Key Factors Leading to Recommended Classification of inorganic bromide salts:
*(figures and tables mentioned in the comments can be viewed in the attachment provided.)

Beneficial Role of Sodium Bromide based bromine antimicrobials in Water Systems
Sodium bromide plays a critical role in controlling micro-organisms in water systems, such as in cooling water and processing systems and production processes such as paper and steel. Cooling and processing waters are ideal environments for growth of microbes and controlling contamination is a constant challenge. Implications that result from micro-organisms that grow in water systems of various manufacturing environments, IT infrastructure, power generation plants, hospitals and other larger residential and commercial buildings include:
• Risk to human health - Creation of suitable environment for pathogens that may pose a public health threat (Legionnaires disease is commonly associated with uncontrolled cooling water)
• Asset integrity - Premature replacement of equipment, unscheduled maintenance, or downtime due to corrosion and plugging
• Degradation of treatment chemicals
• Increased energy consumption (higher pump pressures)
• Loss of cooling capacity (reduced heat transfer)
• Microbiologically influenced corrosion
• Loss in production
Water systems are very dynamic and a variety of biological control tools, e.g., biocides, are needed to manage these systems. The selection of the right treatment method and strategy is critical. These are some of the variables that must be considered when selecting the right biocide:
• Type of water system
• Type of water (well, river, lake)
• pH, temperature, flow rate, operational conditions, etc.
• Contamination types – organic vs inorganic
• Environmental – discharge limits, point of discharge, etc.
Bromine based antimicrobial technologies derived from sodium bromide are very important

oxidizing biological management tools that are particularly effective and applicable in high pH environments. Bromide derived antimicrobial chemistries are the option of choice for these types of applications, with very limited alternatives. Lack of suitable alternatives may compromise biological management efficacy, at a potentially higher cost. A notable advantage of oxidizing chemistries, such as hypobromous acid, is that resistance among biological populations is rare. Bromine chemistry is broadly used across the EU and is the preferred choice due to its ease of use, low cost, wide spectrum of kill and rapid mode of action.

Minimal Exposure During Use
The use of sodium bromide in biocide applications in water systems is unlikely to result in any oral, inhalation, or dermal exposure to humans. It is:
• non-volatile
• targeted delivery to use sites in ways that prevent exposure, e.g., in intermediate bulk containers (IBC, also known as totes) and in solid tablet or granulated form
• applied to water systems using controlled dispensing systems
This situation is somewhat analogous to that of chemical intermediates. Specifically:
"…most chemicals do not have a full set of studies which allow classification and categorisation in all eight health hazards and safe doses for all situations, yet they find a variety of uses. One reason for this is that for some uses it is not necessary to have a complete profile; for instance, chemical intermediates which are never isolated are not considered to need a full package, because human exposure in terms of number of people and dose will be very limited. (Ball et al. 2022)
Clearly, human exposure to sodium bromide in such applications "in terms of people and dose will be very limited." Thus, special consideration of hazard is warranted.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Final comments - Sodium Brommide - CLH (2 June 2023).pdf

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	France		MemberState	4

Comment received

The way the file is structured does not necessarily help with understanding. We think it would be more relevant to describe the systemic effects first, then the effects on "the sexual function and fertility" or "development".

We would appreciate if more details could be added in the read across approach. Indeed, in the TK summary, some table with more details could be added (with chemical structure, solubility values…).

We note that detailed data are included in the annex I, but in our view, a table summarizing the effects of the different substances would have provided a cross-sectional view of the dossier

Endocrine disruption properties:
Regarding effect on thyroid, there are indications that bromides could have endocrine disrupting properties.
In the CLH report, it is clear that bromides have adverse effect on the thyroid (STOT RE justification on thyroid).

For information, in 2019, the active substance 2,2-Dibromo-2-cyanoacetamide (DBNPA) has

been assessed for its endocrine properties and DBNPA fulfils the criterion (d) of Article 5(1) for human health. The endocrine disrupting effects of DBNPA are attributed to the bromide ion (Opinion of the Biocidal Products Committee on the application for approval of the active substance 2,2-Dibromo-2-cyanoacetamide (DBNPA) for product type 4). The documents are available on : https://echa.europa.eu/fr/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1224/PT04

The COMMISSION IMPLEMENTING DECISION (EU) 2023/459 was released on the 2nd of March 2023, not approving 2,2-Dibromo-2-cyanoacetamide (DBNPA) as an existing active substance for use in biocidal products of product-type 4 in accordance with Regulation (EU) No 528/2012 of the European Parliament and of the Council.
Moreover, it seems interesting to compare these effects with those observed for fluoride and chloride. FR is currently evaluating fluoride, for its endocrine disrupting properties on thyroid.
Halogenated compounds seem to have the same effects on the thyroid.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	France		MemberState	5
Comment received				
FR agrees with the classification Repr. 1B, H360FD. Could you please specify which endpoint value was taken into account when estimating the ED10 and what is the justification? FR agrees with the classification Lact., H362.				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	United Kingdom	Health and Safety Executive	National Authority	6
Comment received				
Reproductive toxicity – adverse effects on development We note that, in the pre-natal developmental toxicity studies with ammonium bromide and one pre-natal developmental toxicity study with sodium bromide (Study report, 1995; Study report, 2000b; Study report, 2007), malformations were reported at doses that also caused maternal toxicity. We would welcome a discussion about the maternal toxicity and its impact on the relevance of the malformations for the proposed Category 1B classification.				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	United Kingdom	Health and Safety Executive	National Authority	7
Comment received				
Reproductive toxicity – adverse effects on development We note that, in the pre-natal developmental toxicity studies with ammonium bromide and one pre-natal developmental toxicity study with sodium bromide (Study report, 1995; Study report, 2000b; Study report, 2007), malformations were reported at doses that also caused maternal toxicity. We would welcome a discussion about the maternal toxicity and its				

impact on the relevance of the malformations for the proposed Category 1B classification.

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2023	Austria	The International Bromine Council BSEF	Industry or trade association	8

Comment received

The International Bromine Council BSEF is of the opinion that the reproductive effects observed in rat studies, which form the basis of the proposed Repr. 1B; H360 FD, classification for sodium bromide, are not directly relevant to humans. These effects appear in rats at plasma levels which, in humans, cause severe neurotoxicity. Based on new information confirming the differences in the sensitivity towards bromide-related hazards in rats and humans and which raises doubt about the relevance and transferability of the findings made in rodents to humans, a classification as Repr. 2; H361 f, and a non-classification for developmental toxicity is considered more appropriate, in accordance with chapter 3.7.2.1.1 of the CLP Regulation (EC 1272/2008: "Category 1B Presumed human reproductive toxicant The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate." In addition, Chapter 3.7.2.3. of annex I Weight of evidence is relevant for this data and should be applied accordingly, 3.7.2.3.2: "Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may provide relevant information which reduces or increases concerns about the hazard to human health. If it is conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified." This paragraph clearly applies to the bromide salts in our opinion.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment BSEF detailed comments on KEMI CLH report NaBr_2023-06-01.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH Report NaBr - Supporting studies for CL.zip

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	9

Comment received

The DE CA supports the proposed classification of sodium bromide as Repr. 1B (H360FD) and Lact. (H362).

Fertility:
In accordance with the DS, the criteria for classification in Repr. 1B for adverse effects on sexual function and fertility are considered fulfilled based on the clear evidence of dose related effects on impaired fertility noted in the male and female rats in studies with sodium bromide which are not considered a secondary consequence of general systemic toxicity. Moreover, there was evidence from studies in rats of effects on male reproductive organs

and on female gonads in the absence of severe systemic toxicity.

Development:
In accordance with the DS, the criteria for classification in Repr. 1B for adverse effects on the development of offspring are considered to be fulfilled for sodium bromide: There is clear evidence of adverse dose-related effects on the development of offspring recorded in animal studies with sodium bromide. These include visceral and skeletal malformations and some evidence of increased pup mortality and retarded growth in treated rats. It is furthermore supported that a classification as Repr. 1A is not warranted based on the available human studies, because observed effects of neonatal bromism were reported to be transient.

Lactation:
The view of the DS is supported that classification for effects on or via lactation is considered warranted based on an overall weight of evidence assessment. In non-guideline studies with sodium bromide it was shown that bromide can be transferred via mothers` milk to their pups. Milk production was decreased and the elementary composition of the milk was changed resulting in malnutrition and lowered viability of pups. Thus, there is evidence from animal studies and also weak indication from a human case report that bromide may cause harm due to its effects on and via lactation.

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	United Kingdom	<confidential>	Company-Downstream user	10

Comment received

Essentiality for Health
Research Supporting Essentiality

Essential nutrients are substances required for optimal health. These must be obtained from the diet because they are not formed metabolically within the body. (Greene and McAdam 1983)

The available data indicate that bromine (and its reduced form bromide) should be considered an essential nutrient. Anke et al. (2005) conducted the most extensive examination of bromine deficiency using goats as the model. They showed that bromine deficiency:
• Decreased the success of first insemination and the conception rate, and increased the abortion rate significantly
• Rapidly caused a significantly reduced haemoglobin level a, accompanied by an increasingly lower haematocrit value, suggesting that bromine is either directly or indirectly needed for haemoglobin synthesis;
• Led to significantly lower feed intake, growth rate, and reproduction performance of offspring.
McCall et al. (2014) investigated the importance of bromine in the assembly and integrity of basement membranes, specialized extracellular matrices that provide structural support and mediate intercellular signal transduction in epithelial cells. Using Drosophila as a species whose requirement of bromine is well established, they conducted careful biochemical studies that showed that the assembly of sulfilimine-crosslinked collagen IV scaffolds requires bromine. Although this initial work came from studies in Drosophila, sulfilimine-crosslinked collagen IV scaffolds are essential to the form and function of basement membranes in humans. The crosslink stabilizes newly constructed collagen IV scaffolds, affecting scaffold assembly basement membrane thickness. Because sulfilimine formation

involves the activity of collagen IV, peroxidasin, oxidant, and bromine are all thus critical for basement membranes assembly and tissue development.

Recommended Daily Intake

Regarding the recommend daily intake to maintain human health, Anke et al. (2005) stated:

"The daily normative bromine requirement of adult humans (500 ug/day on the average of a week) is derived from the experiments with animals. The recommended bromine intake by adults, amounting to 2000 µg/day (33 µg/kg/day), is also satisfied by foodstuffs and water." (Anke et al. 2005)

Ubiquity in the Environment

Bromine is abundant in nature as bromide salts or as organobromine compounds (produced by marine organisms). Bromine is also present in rock and the earth's crust. The most used bromine products for industrial purposes are soluble salts found in seawater (~65 ppm), salt lakes, inland seas, and brine wells (2,500 to 10,000 ppm). Sea water contains bromine in about 65 parts per million (ppm), but bromine is found in much higher concentrations (2500 to 10,000 ppm) in inland seas and brine wells. (AZO Materials 2006)

Given its ubiquity in the environment, human exposure to bromine is universal. Various estimates can be found, but the following are most relevant:

• Chronic adult (middle bound estimate) = 0.33 mg/kg/day – Based on European Food Safety Authority by combining EU food consumption information from dietary with data for pesticide residues per food commodity (European Food Safety Authority (EFSA) 2019) and as presented by the Danish Environmental Protection Agency (2021) (Danish Environmental Protection Agency (DEPA) 2021)

• Chronic Intake by adults = 2.3 and 6.8 mg/day (0.038 and 0.113 mg/kg/day) reported by Anke et al. (Anke et al. 2005) citing a global literature survey of Human dietary intakes of trace elements (1971-1990) by the International Atomic Energy Agency.

Special Considerations for Classification

The essentiality of bromine requires a different look at the hazard assessment and related exposure assessment and risk characterisation. Although the focus is still on hazard, acknowledgement of its ubiquity in the environment and essentially universal human exposure is legitimate. The goal of zero human exposure is neither realistic, nor necessary. With respect to non-cancer effects, practical thresholds exist below which toxicity does not occur. In contrast for essential elements such as bromine the threshold of most concern is one below which toxicity results from a deficiency. This requires a different view of the entire risk assessment exercise. Rather than attempting to reduce exposures to zero, based on a presumption that risk exists from any exposure or above a certain threshold, it is important to realize that the background exposures that occur in a population are necessary for health.

Figure 2 shows the special Dose-Response Relationship associated with essential nutrients.

Figure 2*: Special Dose-Response Relationship for Essential Nutrients

*(figures and tables mentioned in the comments can be viewed in the attachment provided.)

Most notable, a decreasing nutrient level results in a decrease in the adverse effect response to a point well above zero dose that reflects the threshold for an adverse response. This is the inflection point in the curve below which lies the region of homeostasis. A continued reduction in nutrient levels results in another inflection point at which further reduction in nutrient level results in toxicity from nutrient deficiency. Thus, in contrast to many regulated chemicals, humans can have too little bromine in their body. Figure 3 shows a compilation of various Allowable Daily Intake levels and human exposure parameters. The bars represent ADIs for bromine in various chemical forms as established

by various regulatory and scientific bodies (European Medicines Agency (EMEA) 1997, 1999; FAO/WHO 1989; Food Safety Commission of Japan (FSCJ) 2015; National Sanitation Foundation (NSF) 2011; van Leeuwen et al. 1983; United States Environmental Protection Agency (USEPA) 2010). The chronic human intake level (middle bound comes) from the EFSA (European Food Safety Authority (EFSA) 2019) and the Danish EPA (Danish Environmental Protection Agency (DEPA) 2021). The recommended daily intake was put forth by Anke et al. (2005).

Figure 3*: Allowable Daily Intake levels and human exposure parameters for various forms of bromine
*(figures and tables mentioned in the comments can be viewed in the attachment provided.)

Table 1*: Legend for Figure 3 (Allowable Daily Intake levels and human exposure parameters for various forms of bromine)
*(figures and tables mentioned in the comments can be viewed in the attachment provided.)

(European Medicines Agency (EMEA) 1997, 1999; FAO/WHO 1989; Food Safety Commission of Japan (FSCJ) 2015; National Sanitation Foundation (NSF) 2011; van Leeuwen et al. 1983; United States Environmental Protection Agency (USEPA) 2010)
The graph clearly shows the human intake is above the recommended daily intake, thereby avoiding any deficiency. It is also important to note that the chronic human intake is well within all the ADIs presented, indicating that present and incremental exposure increases pose no hazard to humans.

Conclusions
The current proposal for classification of Sodium Bromide in Category Reproductive 1B is based on rationale that the adverse effects seen in high dose animal studies could be relevant to humans. A review of the details of the use of Sodium bromide as a biocide to control micro-organisms in water systems shows that this should be reconsidered because:
1) Sodium bromide is a critical part of a biocidal programme to control micro-organisms in water systems. It is non-volatile, is delivered to use sites in ways that prevent exposure and are applied to water systems using controlled dispensing systems. Thus, it is unlikely to cause any oral, inhalation, or dermal exposures to humans that are of toxicological significance.
2) Besides its ubiquity in the environment, bromine (and the reduced form bromide) is an essential trace element that provides vital benefits to humans at low doses. Allowable daily intake levels have been established for bromine that maximum exposure levels that are safe. Typical human exposures result in a beneficial human response versus an adverse human response.

Based on the factors cited and detailed in our comments above, a Category 2 Classification for Reproductive Toxicity is more appropriate.

References are provided in the attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Final comments - Sodium Brommide - CLH (2 June 2023).pdf

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment

				number
02.06.2023	France		MemberState	11
Comment received				
FR agrees with the classification STOT SE 3, H336				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	12
Comment received				
The proposed classification as STOT SE 3 is supported based on transient CNS effects in humans and supporting evidence of transient narcotic effects in animal studies.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2023	Austria	The International Bromine Council BSEF	Industry or trade association	13
Comment received				
The International Bromine Council (BSEF) agrees that the toxicity of the bromide ion is characterized by neurotoxicity and that humans have been shown to be more sensitive to bromide-induced neurotoxicity than rats. A revisit of the available human data demonstrates that following conversion of blood levels to a dose in mg/kg bw/day, the dose levels which cause neurotoxicity in humans are largely observed at doses which do not qualify for a classification into category 1 for STOT RE. Bromide-related neurotoxicity may start at blood levels of 6 – 12 mmol/L corresponding to about 32 – 64 mg/kg bw/day based on a body weight of 60 kg and assuming a blood volume of 4 L. The cut off limit of STOT RE 1 is 10 mg/kg bw/day for a 90-day exposure period equivalent to 2.5 mg/kg bw/day in humans following correction for allometric scaling. In the available human case studies, e.g. the observations made in pregnant women, the exposure duration was longer than 13 weeks. In the study of Sangster (Sangster et al., 1983), mild effects on neurophysiological function were observed at 4 mg/kg bw/day after 3 months. This dose is above the cut-off limit of 2.5 mg/kg bw/day adjusted for allometric scaling. Based on the weight of the evidence from human studies, a classification with STOT RE 2; H373 (nervous system) is, therefore, more appropriate. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BSEF detailed comments on KEMI CLH report NaBr_2023-06-01.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH Report NaBr - Supporting studies for CL.zip				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	14
Comment received				
The proposed classification as STOT RE 1 with the nervous system as target organ is supported based on the available human data on bromism (case reports) with supporting animal data. The effects on the thyroid are not considered severe enough for it to be included as target organ.				

Date	Country	Organisation	Type of Organisation	Comment

				number
02.06.2023	France		MemberState	15
Comment received				
FR agrees with the classification STOT RE 1, H372 (nervous system). Regarding STOT RE for thyroid effects, we agree on the fact that : ”In this case of sodium bromide and bromide salts, histopathological changes (i.e. follicular hypertrophy and/or hyperplasia) in the thyroid, and changes in the circulating levels of thyroid hormones have been reported. Thus, human relevance of thyroid disruption of ammonium bromide cannot be ruled out.” Therefore, could you please provide a robust justification explaining why the Sodium bromide is not considered as STOT RE Thyroid? (This comment joins the one on endocrine disruptor hazard).				

PUBLIC ATTACHMENTS
1. Final comments - Sodium Brommide - CLH (2 June 2023).pdf [Please refer to comment No. 3, 10]
2. BSEF detailed comments on KEMI CLH report NaBr_2023-06-01.zip [Please refer to comment No. 2, 8, 13]

CONFIDENTIAL ATTACHMENTS
1. CLH Report NaBr - Supporting studies for CL.zip [Please refer to comment No. 2, 8, 13]